

Claims

- 5 1. A method for determining a predisposition for a manifestation of an immune system related disease in an individual comprising determining in a biological sample isolated from said individual the presence or absence of a polymorphism within the amino acid sequence of the MASP-2 protein as identified in SEQ ID NO: 1 and/or within the amino acid sequence of the MAp-19 protein as identified in SEQ ID NO: 2, said polymorphism being a substitution, deletion and/or
10 addition of at least one amino acid residue.
2. The method of claim 1, wherein the polymorphism a substitution, deletion and/or addition of at least one amino acid within a fragment of MASP-2 consisting of CUB1, EGF, CUB2, CCP1 and CCP2 domains.
- 15 3. The method of claim 1, wherein the polymorphism being a substitution, deletion and/or addition of at least one amino acid within a fragment of MASP-2 and/or MAp-19 consisting of CUB1, EGF, CUB2 domains.
- 20 4. The method of claim 1, wherein the polymorphism being a substitution, deletion and/or addition of at least one amino acid within a fragment of MASP-2 and/or MAp-19 consisting of CUB1.
- 25 5. The method according to any of the preceding claims, wherein the polymorphism being a substitution, deletion and/or addition of at least one amino acid located within amino acid residues from position 80 to position 120 according to the amino acid sequences set forth in SEQ ID NO: 1 or 2.
- 30 6. The method according to any of the preceding claims, wherein the polymorphism being a substitution or deletion of Asp in position 105 according to the amino acid sequences set forth in SEQ ID NO: 1 or 2.
7. The method of claim 6, wherein the substitution being Asp→Gly.
- 35 8. A method for determining a predisposition for a manifestation of an immune system related disease comprising determining the presence or absence of

polymorphism within the coding DNA sequence (SEQ ID NO: 3) of the human MASP-2 gene, said polymorphism being a substitution, addition or deletion of at least one nucleotide within said coding DNA sequence.

- 5 9. The method of claim 8, wherein the DNA sequence comprising the polymorphism is a coding nucleic acid sequence for the proteins as defined in any of the claims 1-7.
- 10 10. The method of claim 8, wherein the polymorphism being a single nucleotide substitution/mutation A→G in position 359 corresponding to the sequence set forth in SEQ ID NO: 3.
- 15 11. The method according to any of the claims 1-10, wherein the polymorphism is determined by isolating the MASP-2 and/or MASP-19 proteins from a biological sample collected from an individual and ascertaining the substitution/mutation in the amino acid sequence of said proteins by a method selected from the group comprising mass-spectroscopy methods, such as MALDI-TOF mass-spectroscopy, protein sequencing methods or immunoassays.
- 20 12. The method according to any of the claims 1-11 further comprising isolating the MBL-MASP or ficolin-MASP complexes from a biological sample collected from an individual and examining the activity of said complexes, said activity being determined as an ability the complexes to activate the C4 complement.
- 25 13. The method according to any of the claims 1-12 further comprising examining the protein composition of MBL or ficolin complexes in a biological sample collected from an individual.
- 30 14. The method according to any of the claims 1-13, wherein the predisposition to a manifestation of an immune system related disease is determined by the absence of the MASP-2 (SEQ ID NO: 1) and/or MASP19 (SEQ ID NO: 2) proteins in the MBL or ficolin complexes.
- 35 15. The method according to claims 8-10, wherein the presence or absence of the polymorphism is detected by hybridising a probe to a target nucleic acid

sequence comprising at least position 359 according to the SEQ ID NO: 3 or SEQ ID NO: 4 or the corresponding position of the complementary strand.

- 5 16. The method according to claim 15, wherein the probe is bound to a detectable label.
- 10 17. The method according to claim 16, wherein the label is selected from a group comprising fluorescent reporter groups, enzyme tags, chemiluminescent groups or radioisotopes.
18. The method according to claim 15, comprising the use of a capture probe for capturing a target nucleic acid sequence.
- 15 19. The method according to any of the preceding claims 15-18, comprising amplification of a nucleotide sequence comprising the polymorphism.
20. The method according to claim 19, wherein amplification comprises use of a primer pair comprising SEQ ID NO: 5 and 6 or SEQ ID NO: 7 and 8.
- 20 21. The method according to claim 8, wherein the presence or absence of the polymorphism is detected by using isolation of a target nucleic acid from an individual said target nucleic acid comprising at least position 359 according to the sequence set forth in the SEQ ID NO: 3 or the corresponding position of the complementary strand and sequencing of said isolated target nucleic acid.
- 25 22. The method according to any of the claims 8-21, further comprising assessing the alleles at nucleotide no. 359 according to the sequence set forth in SEQ ID NO: 3 in a target nucleotide sequence corresponding to SEQ ID NO: 3 or the complementary strand.
- 30 23. An isolated oligonucleotide comprising at least 10 contiguous nucleotides of SEQ ID NO: 3 or the corresponding complementary strand, said nucleic acid sequence comprising the G allele in position 359 or the corresponding allele of the complementary strand.
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24. The isolated oligonucleotide according to claim 23, comprising at least 15 contiguous nucleotides, more preferably at least 20 nucleotides.
25. An isolated polynucleotide sequence encoding the MASP-2 polypeptide having Gly at position 105 according to amino acid sequence set forth in SEQ ID NO: 1.
26. An isolated polynucleotide sequence encoding the MAP-19 polypeptide having Gly at position 105 according to amino acid sequence set forth in SEQ ID NO: 2.
27. The isolated oligonucleotide or polynucleotide sequence according to any of the claims 23-26, wherein the nucleotides are selected from RNA, DNA, LNA, PNA monomers or chemically modified nucleotides capable of hybridising to a target sequence.
28. An isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1 or a fragment thereof, said polypeptide or said fragment comprising Gly in position 105 according to said sequence.
29. An isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2 or a fragment thereof, said polypeptide or said fragment comprising Gly in position 105 according to said sequence.
30. An isolated peptide fragment having a size in a range from 5 to 160 amino acids derived from the amino acid sequence set forth in SEQ ID NO: 1 comprising at least 5 amino acid contiguous sequence, said sequence corresponding to amino acid residues 100-105, 101-106, 102-107, 103-108, 104-109 and/or 105-110 of the sequence set forth in SEQ ID NO: 1.
31. An isolated peptide fragment having a size in a range from 5 to 160 amino acids derived from the amino acid sequence set forth in SEQ ID NO: 1 comprising at least 5 amino acid contiguous sequence, said sequence corresponding to amino acid residues 100-105, 101-106, 102-107, 103-108, 104-109 and/or 105-110 of the sequence set forth in SEQ ID NO: 1, wherein Gly in position 105 of said sequence is substituted for Asp.

32. An isolated antibody capable of recognition of the MASP-2 and/or MAP-19 polypeptides or fragments thereof, said polypeptides and fragments comprising Gly in position 105 according to the SEQ ID NOS: 1 or 2, by selectively binding to an epitope comprising said Gly or selectively binding to an epitope created within said polypeptides or said fragments due to mutation of Asp→Gly in position 105 according to SEQ ID NOS:1 or 2.
33. An isolated antibody capable of recognition of the MASP-2 and MAP-19 polypeptides or fragments thereof by selectively binding to an epitope comprising Asp corresponding to position 105 of the sequence set forth in SEQ ID NOS: 1 or 2.
34. A kit for predicting an increased risk of a subject of developing an immunologic disease comprising at least one probe comprising a oligonucleotide sequence as defined by any of the claims 23-27 and/or at least one probe comprising at least one antibody as defined by claims 32 and 33, or a fragment of said antibody.
35. The kit according to claim 34, wherein the probe is linked to a detectable label.
36. The kit according to any of the claims 34-35, further comprising a set of primers for amplifying a region of the human MASP-2 gene said region comprising position 359 according to SEQ ID NO: 3 or the corresponding complementary strand.
37. A gene therapy vector for the treating pathologic conditions associated with low activity of MBL-pathway in a subject carrying the G allele in the position corresponding to nucleotide no 359 of the sequence identified in SEQ ID NO: 3.
38. The gene therapy vector of claim 37, said vector comprising the sequence set forth in SEQ ID NO: 3, or a fragment thereof operably linked to a promoter sequence capable of directing the in vivo expression of MASP-2 encoded by SEQ ID NO: 3.
39. A gene therapy vector for the treating therapeutic conditions associated with pathologically high activity of the MBL-pathway, said vector comprising the

nucleotide sequence identified as SEQ ID NO: 3, said sequence having substitution A→G in position 359, said sequence operably linked to a promoter sequence capable of directing the in vivo expression of MASP-2 having glycine residue in position 105 according to the sequence set forth in SEQ ID NO: 1.

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40. Use of a polypeptide comprising any of the amino acid sequences set forth in SEQ ID NOS: 1 or 2, or fragments thereof, said polypeptides or said fragments comprising Gly in position 105 of said sequences, for production of a medicament for the inhibition of activity of the lectin-complement pathway.

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41. Use of a peptide fragment according to claim 40 for inhibition of activity of the lectin-complement pathway.

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42. Use of a polypeptide comprising any of the amino acid sequences set forth in SEQ ID NOS: 1 or 2, or fragments thereof, said polypeptides or said fragments comprising the glycine residue in position 105 of said sequences for the manufacture of a medicament for treatment of therapeutic conditions associated with pathologically high activity of the lectin-complement pathway.

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43. Use of an oligonucleotide and/or polynucleotide as defined in any of the claims 25-28 for the manufacture of a medicament for treatment of therapeutic conditions associated with pathologically high activity of the lectin-complement pathway.

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44. Use of an antibody as defined in claim 33 or a fragment thereof for the manufacture of a medicament for treatment of therapeutic conditions associated with pathologically high activity of the lectin-complement pathway.

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45. The use according to claim 42-44, wherein the therapeutic conditions associated with pathologically high activity of MBL-complement pathway being an inflammatory disease, ischemia, apoptosis or atherosclerosis.

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46. A method of treatment of an individual having a predisposition to a manifestation of an immune system related disease comprising
I) identification a mutation in the MASP-2 gene of said individual and

- II) administering to said individual an effective amount of a polypeptide comprising SEQ ID NO:1 and/or polypeptide comprising SEQ ID NO:2.